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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/778,672	02/07/2001	Hsu Ching-Hsaing	12774-002001	4367

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/778,672	Applicant(s) CHING-HSAING ET AL.	
	Examiner Q. Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-33,35-39 and 41-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-33,35-39 and 41-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed 2/3/03 have been entered as Paper No. 17. Claims 24, 35, 36, 43, and 44 have been amended, claims 34 and 40 have been canceled, and claims 46-49 are newly submitted. Claims 24-33, 35-39, and 41-49 are pending in the application and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 24-45 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment and arguments.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejection of claims 24, 34 and 35 under 35 U.S.C. 112, second paragraph, is withdrawn in view of the claim amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 25, 28-33, and 43 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Hsu et al* (US 5,958,891), in view of *Medaglini et al* (PNAS 1995;92:6868-72, IDS/AI).

The arguments presented in paper #17 have been fully considered, but they are not persuasive, and will be addressed point-by-point as follows.

Applicants argue that there was no expectation of success for the substitution (of the plasmid pSMB7-M6 with the pCMV-Der p5) suggested by the Examiner, because the pCMV-Der p5 is a eukaryotic expression construct for expression of Der p5 in mammalian cells, not for expression in a bacterial cell, such as the *Streptococcus gordonii.*

With regard to the expression construct, both *Hsu et al* and *Medaglini et al* references use a plasmid as vector, and it is known in the art that a plasmid could be introduced and functioning in mammalian cells, as well as bacterial cells, and it can be found in a variety of bacterial, fungal and plant cells. Therefore, the difference of the

constructs between *Hsu et al* and *Medaglini et al* would be the promoter used in the plasmid.

With regard to the promoter, first, it is noted that the claims as written encompass using any type of promoter including the promoter used in the pSMB7-M6, there is no limitation concerning the type of promoter in the claim; second, the instant specification teaches that a bacterial promoter could be used in the invention, such as the erythromycin resistance gene promoter, and IdhL promoter (Specification, page 2, line 4), and newly submitted claim 46 explicitly calls for using promoters of bacterial origin. Apparently, at the time of the filing and currently, Applicants have not considered the eukaryotic promoter is a crucial element for practicing the instant invention, and thus, the argument is conflicting with what is now claimed. Thirdly, the claims require "expressing the allergen in the subject", which encompasses expressing the allergen in mammalian cells. Fourthly, *Medaglini et al* use *Streptococcus gordonii* as a delivery vehicle carrying the pSMB7-M6 plasmid, and successfully expressed a recombinant allergenic protein in the mice. Evidently, the pSMB7-M6 could express allergic proteins in a subject, and thus, meets the claim limitation. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Medaglini et al,* by simply substituting the M6 with the Der p5 as taught by *Hsu et al* with a reasonable expectation of success.

Applicants next argue that Medaglini's method does not disclose or suggest a system for suppressing IgE production, rather, they teach a method that induces IgA and IgG immune response. Thus, one skilled in the art intending to suppress IgE

production, would not have been motivated to use a system that induces IgA and IgG production.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, *Hsu et al* teach a method of suppressing the allergen-specific IgE production in a subject comprising administering to the subject a recombinant plasmid comprising a CMV promoter (constitutive) operably linked to a sequence encoding an allergen. *Hsu et al* also teach the mechanism of IgE suppression, i.e. the delivered allergen (antigen) could induce the production of Ag-specific CD8+ T cells and modulate/suppress IgE synthesis (column 2, line 54). Therefore, suppressing of IgE production relies on inducing a different type of immune response. *Medaglini et al* teach a general system that allows for the stable expression of a wide range of protein antigens on the surface of non-pathogenic Gram-positive commensal bacteria. The exemplified embodiment is *Streptococcus gordonii* engineered to surface expressing an allergen from hornet venom (M6 protein). They teach that the advantage of their system is using a bacteria that is live and non-pathogenic, yet maintaining certain invasive/adherence qualities to induce an immune response (Introduction, page 6868), they teach the system has a general applicability for deliver foreign antigens to a mammalian host because the prolonged exposure of the immune system to a recombinant antigen achieved by the stable colonization of a recombinant commensal is

a safe and efficient way of overcoming the need for repeated doses of antigen (paragraph bridging left and right columns in page 6872. The exemplified production of antigen-specific IgA and IgG is "as a proof of the general applicability" (first paragraph, right column, page 6868). Therefore, the system does not conflicting with the method of *Hsu et al*, only enhancing the efficiency of delivered nucleic acids. Applicants are reminded that *Medaglini et al* reference is relied upon for general application of using live gram-positive bacteria as a nucleic acid delivery vehicle, which would enhance the immune response of the nucleic acid that they carried on. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of *Hsu et al* and *Medaglini et al,* by using the delivery vehicle provided by *Medaglini et al* in the delivery of the Der p5 with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the non-pathogenic bacterial system could express the allergen stably, and using oral delivery route is less painful for

patients. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 24-33, 35-39, and 41-45 stand rejected, and claims 47-49 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Hsu et al* (US 5,958,891) and *Medaglini et al* (PNAS 1995;92:6868-72) as applied to claims 24, 25, 28-33, and 43 above, and further in view of *Casas et al* (US 6,100,388) and *Kailasapathy et al* (Immunol and Cell Biol 2000;78:80-88).

In paper #17, Applicants argue that the combination of *Hsu and Medaglini* does not suggest a method as presently claimed, Casas does not disclose using lactobacilli to suppress IgE production, and Kailasapthy does not disclose using lactobacilli to deliver an antigen to suppress IgE production.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the arguments drawn to the combination of *Hsu and Medaglini* have been addressed in the immediate preceding section. *Casas et al* reference was relied upon as a showing of using *Lactobacilli* as a vaccine delivery vehicle, and the vaccine could be ingested orally in milk products (abstract), such as yogurt (column 1, line 49). *Kailasapathy et al* reference was relied upon as a showing for the therapeutic potential using probiotic organisms with particular emphasis on

Lactobacillus, and *Bifidobacterium.* (see entire article particularly abstract), and a showing that it is known to the skilled artisan that such therapeutic benefit has seen in reduction of food allergy. Applicants are reminded that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Accordingly, for reasons of record and those set forth above, the rejection stands.

Claims 24-33, 35-39, and 41-49 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Hsu et al* (US 5,958,891), *Medaglini et al* (PNAS 1995;92:6868-72), *Casas et al* (US 6,100,388), and *Kailasapathy et al* (Immunol and Cell Biol 2000;78:80-88) as applied to claims 24-33, 35-39, 44-49 above, and further in view of *Pouwels et al* (J Biotechnol 1996;44:183-92, IDS/AG).

Claim 46 is drawn to promoters of bacterial origin, such as an IdhL promoter. The combined teachings of *Hsu et al, Medaglini et al*, *Casas et al*, and *Kailasapathy et al* do not teach the particular promoter(s).

Pouwels et al teach that the Idh promoter of Lactobacillus (IdhL) could be used in the expression construct in the context of using *Lactobacillus* as a carrier for oral immunization.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the combined teachings of *Hsu et al, Medaglini et al*, *Casas et al*, and *Kailasapathy et al* by using an IdhL promoter in the genetic construct with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it is known in the art that this promoter is efficient in expressing a heterologous protein for vaccine purpose. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
April 7, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER